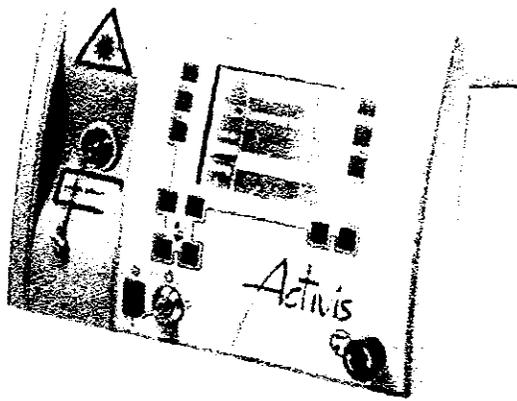


Activis

RED 689nm LASER



OPHTHALMIC PHOTOACTIVATOR

USER MANUAL DRAFT



93/42/EEC Directive

XL ACTI ME US

MARCH 2006

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1 - WARNINGS AND CAUTIONS

This manual is designed to acquaint you with the normal operation and maintenance of the ACTIVIS, red 689 nm PDT laser ophthalmic photoactivator.

The scope of this manual is limited to the operation and maintenance of the instrument and its controls and is not intended to be a guide for the treatment of disorders where ophthalmic laser photoactivation is indicated.



CAUTION: Federal (USA) law restricts this device to sale to or use by licenced professionals.



CAUTION: Use of controls or adjustments or performance of procedures other than those specified herein may result in hazardous radiation exposure.

The safe use of this laser system begins with your understanding that this laser system:

- 1 is classified as a class IIIb system, and as such has sufficient energy that the direct or reflected beam is hazardous to the eye and skin,
- 2 is a fire hazard when operated near flammable or explosive material,
- 3 activates a photochemical process that produces controlled destruction of living tissue.



All personnel except the operator must wear protective eyewear to eliminate the risk of eye damage.

Misuse of the laser system may result in accidental injury to the patient, physician or attendants.

Users should thoroughly understand this manual and laser safety standards before operating the laser, and always keep the manual handy. Personnel working in the laser hazard area must receive periodic training. The ACTIVIS systems are intended only for physicians skilled in photodynamic treatment of retinal diseases.

The American National Standard for the Safe Use of Lasers in Health Care Facilities (**ANSI Z 136.3 -1996 and ANSI Z 136.1 - 1993**) provide guidance for the safe use of lasers and lasers systems in diagnostic and therapeutic areas. It outlines the facility requirements, the administrative and the procedural measures needed to minimize and confine the laser hazard, based on the Nominal Hazard Zone, the space where the level of direct, reflected, or scattered radiation during normal operation exceeds the Maximum Permissible Exposure limits.



1 - WARNINGS AND CAUTIONS

These measures include: personnel training and supervision, proper warning signage around and access control to the controlled laser zone (treatment room), beam containment within the controlled laser zone (using screens and barriers), and minimizing unprotected exposure (with protective eyewear and clothing, door interlocks etc.).

The owner and operator are responsible for ensuring such ANSI safety measures are taken, in consultation with their Laser Safety Officer. See also Section 3-4 Laser Safety Eyewear, Section 4-1 Safety procedures during use and Section 6-3 Recommendations for the Room Installation, in this manual.

Power density at the treatment site is an important parameter in determining the required light dose needed to produce the desired photodynamic effect. The ACTIVIS system will automatically adjust output to maintain the selected power density over the operating range of spot sizes. However, other parameters (such as lens magnification) must be correctly entered into the system; otherwise laser output may not be safe or effective.

To prevent the risk of electrical shock, and / or exposure to harmful radiation, do not remove the cover. The unit does not contain any user serviceable parts. If needed, the fuses, located in the panel above the power cord socket at the rear, should be replaced with identical models.

Only use Quantel Medical slit lamp adaptors ZSL30 ACT™, ZSL 120 ACT™, HSBMBQ ACT™ with the ACTIVIS laser console.

For service needs, or if you notice a change in laser efficacy, please contact the Quantel medical Service Department or your local distributor.

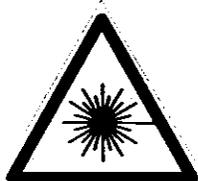
The warranty will be void if the unit is opened (even partially), modified or repaired in any way by persons who are not authorised by Quantel Medical.

Quantel Medical cannot be held responsible for any damage or injury which results from a failure to follow, or incorrect use of the instructions contained in this manual.

You are encouraged to forward all comments or questions regarding the operation, maintenance or the use of this product to Quantel Medical.

 **WARNING:**

<p>100 - 240V~ 50/60 Hz 80 VA in 240V 70 VA in 100V</p>		 <p>$I_{max} = 0.7A$</p>	<p style="text-align: center;">DANGER</p> <p>LASER RADIATION Avoid eye or skin exposure to direct or scattered radiation</p> <hr/> <p>Diode 689 nm 500 mW CLASS IIIb LASER PRODUCT</p>
<p>SURGICAL LASER LASER CLASS 3B / IIIb Laser Diode : 689nm, 500mW Max</p> <p>LASER CLASS 2 / II Laser Diode : 635nm, <1mW Max</p> <p>VISIBLE AND/OR INVISIBLE LASER RADIATION AVOID EYE OR SKIN EXPOSURE TO DIRECT OR SCATTERED RADIATION CLASS 3B LASER PRODUCT as per EN 60825-1:94</p>			



CAUTION: FEDERAL US LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN OR AN OPTOMETRIST LICENCED BY THE LAW OF THE STATE IN WHICH HE PRACTISES TO USE OR ORDER THE USE OF THIS DEVICE

DANGER: EXPLOSION HAZARD. DO NOT USE IN PRESENCE OF FLAMMABLE ANESTHETICS OR IN OXYGEN-RICH ATMOSPHERE.

CAUTION: ELECTRIC SHOCK HAZARD. DO NOT OPEN REFER SERVICING TO QUALIFIED SERVICE PERSONNEL.

 **WARNING:**

- 1) To comply with standard safety requirements for medical electrical equipment, the ACTIVIS system must be plugged into a grounded wall receptacle. Use of an adapter for multiple connections or a power bar is prohibited.
- 2) Do not use a 3-prong plug adaptor to accommodate an ungrounded 2-prong wall receptacle.
see Chapter " 6-3-2 Electrical requirements "



WARNING: Disconnect AC power before or changing the fuses, or cleaning the case : (see Chapter 9, Maintenance).



WARNING: Switch the system off before attaching the fiber optic connector, or when inspecting any system components.



WARNING: Instrument calibration must be performed every year by either by an authorized Quantel Medical technician or by a qualified laser system engineer or technician using the power calibration procedure (Appendix 1). The instrument should be serviced yearly.



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689 nm laser

3 - TECHNICAL SPECIFICATIONS

PARAMETER		DESCRIPTION
LASER BEAM	Laser class	Class IIIb (3b) laser product
	Laser source	Red diode laser 689nm
	Operating wavelength	689 nanometers (nm)
	Output power	4 - 400 milliwatts (out of optical delivery)
	Input power	100-240 V~ ±10%, 50/60 Hz ±3%, single phase (10A minimum)
	Exposure time	20 to 120 seconds
AIMING BEAM	Laser class	Class II
	Laser source	Red diode laser
	Operating wavelength	635nm
	Output power	<0.9 mW
GENERAL	Cooling	Air cooling
	Sizes	Height: 8.1 in (21 cm) Width: 11.8 in (30 cm) Depth: 9.8 in (25 cm) Weight: 11 lb (5 Kg)
INTERFACE CONTROLS	Optical delivery	Slit lamp adaptor
	Key switch	Power supply ON / OFF
	Front panel	Push buttons
	Foot switch	Connected at the back of the unit, redundant switch configuration
	Emergency stop	Cuts power to all user interface controls, disable laser head
	Safety	Internal monitoring of all critical systems including redundant safety circuits to monitor shutter system, power control system and microprocessor control system

3 - TECHNICAL SPECIFICATIONS

Precautions to take to avoid electromagnetic interference with other devices:

The Activis conforms to the IEC 601-1-2 standard (electromagnetic compatibility). Ensure that devices used in the same room are conform to this standard.

Precautions to take when disposing of device and accessories:

Contact QUANTEL MEDICAL for more information. Equipment shipped back to QUANTEL MEDICAL must first be cleaned with a hospital disinfectant and be accompanied by a certification of decontamination.

3-1 COMPLIANCE

- | | |
|--|-----------------------|
| - This device complies as applicable with: | 21 CFR 1040 |
| - European Directive: | 93/42/EEC |
| - Power supply and enclosure designed per: | EN 60-601-1 |
| - Electromagnetic compatibility: | EN 60-601-1-2 |
| - Safety of therapeutic laser equipment: | EN 60 601-2-22 |
| - Safety of laser products: | IEC 825-1 |
| - Electrical leakage below limits: | UL 544 |

3-2 ENVIRONMENTAL CONDITIONS

The temperature of the room where the Laser is operated must be within the range:

$$59^{\circ}\text{F} < T^{\circ} < 86^{\circ}\text{F} \quad (15^{\circ}\text{C} < T^{\circ} < 30^{\circ}\text{C})$$

The relative humidity must not exceed **95%** without condensation.

The Laser storage temperature must be within the range:

$$-4^{\circ}\text{F} < T^{\circ} < 158^{\circ}\text{F} \quad (-20^{\circ}\text{C} < T^{\circ} < 70^{\circ}\text{C})$$

3-3 DELIVERY OPTIONS

Only the following Quantel Medical slit lamp adaptors can be used :

- ZSL30 ACT™ for the Zeiss 30 slit lamp,
- ZSL120 ACT™ for the Zeiss 120 slit lamp,
- HSBMBQ ACT™ for the Haag-Streit slit lamp.



3 - TECHNICAL SPECIFICATIONS

3-4 LASER SAFETY EYEWEAR

Most lasers require that safety eyewear be worn during operation. The need for safety eyewear is based on the Maximum Permissible Exposure (MPE), the Nominal Ocular Hazard Distance (NOHD) and the Optical Density (OD) for the laser emission, and the configuration of the controlled laser zone or treatment room.

The NOHD should be determined by the Laser Safety Officer, for the specific laser. For additional information, refer to ANSI Z136.1-1993, ANSI Z136.3-1996, or European Standard EN 60825: 1992, Appendix A.

The following formula was used to calculate the worst case NOHD for the ACTIVIS laser with its slit lamp adaptor 689 PDT. The values specified here meet or exceed the laser safety eyewear requirements for the slit lamp adaptor.

$$NOHD = \frac{\sqrt{Pf * (4 * Po / (3.14 * E_{MPE}))} - a}{\emptyset} + z$$

where,

- a = the beam waist diameter;
- z = distance between the laser system and the beam waist;
- ∅ = full angle beam divergence;
- Po = maximum laser power available;
- Pf = the profile correction factor;
- E_{MPE} = Maximum Permissible Exposure, in power density units (power per unit area);
- NOHD = the Nominal Ocular Hazard Distance (measured from laser aperture)
- = the distance required to reduce the power density to the MPE.

$$E_{MPE} = 42,25 W / m^2$$

$$NOHD = 10.17 m + 0.30 m \text{ (focusing distance)} = 10.47 m$$

Optical Density for Safety Eyewear:

All personnel who are within the NOHD are considered to be within the controlled laser zone and shall wear eye protection with a minimum optical density (OD) of:

$$\text{O.D.} = -\text{LOG} (E_{\text{MPE}} / \text{Power density}) = 3.45$$

For maximum security, the safety eyewear must have a protection class of L4 (EN 207 Standard).

NOTE: Safety eyewear specifications are determined for each individual model of laser. Eyewear supplied with other systems may not be appropriate for use with the ACTIVIS system.

Laser eyewear should also be resistant to photobleaching (refer to ANSI Z136.1-1993 Section 4.2.6).

Goggles are available from your QUANTE! MEDICAL representative or directly from a recommended vendor (See Appendix 2).

4 - SAFETY PROCEDURES

4-1 SAFETY PROCEDURES DURING USE

This section introduces a few elementary steps to follow when using your photoactivator. Understand and comply with these instructions and the procedures outlined in **ANSI Standard Z136.3** in order to prevent injury to personnel or damage to the instrument.

1. Never look directly into a laser light source, avoid exposure to reflected or scattered laser light. This is a class IIIb laser product. Direct, reflected, or scattered light may produce severe eye injury and / or skin burns.
2. Remove or cover all shiny or metallic reflecting objects within the laser area. Any medical instruments that cross the laser beam must have a shape or surface that prevents reflections. Similarly, surfaces in the laser hazard area including the floor should be non-reflective or covered with non-reflective material.
3. Always require safety glasses for anyone present at a treatment, except for the physician and patient (The physician is protected by the filter on the slit lamp adapter; make sure this is installed and intact). During some procedures it may be advisable to shield untreated eyes.
4. The treatment beam emitted from this instrument is a possible ignition source for flammable materials or explosives. Do not use this system near such materials, including drapes, clothing, anesthetic gases, and some solutions used in surgical preparation.
5. Never leave the system ON when it is unattended. If you must leave, turn the system OFF and take the key with you.
6. When the laser is ON, keep the system in the standby mode except during actual treatment.
7. Only the treating physician should have access to, and depress the foot pedal.
8. Use anti-reflection contact lenses treated for 689nm wavelengths. Contact lenses, particularly those with plano surfaces, can generate dangerous reflections.
9. Observe warnings on all **DANGER**, **WARNING**, or **CAUTION** labels. **Chapter 5** illustrates the location and contents of these labels.

4 - SAFETY PROCEDURES

10. Clearly mark the laser hazard area with appropriate signage. Ensure the entrance is closed before operating the system.
11. Circuitry for connection of a remote interlock is provided. An interlock can be attached to contacts on the laser room door, or to another actuator. If the interlock circuit is broken, the laser will electronically revert to the standby state. This prevents the laser system from firing if the laser room is entered during use.

Similarly, an external red warning light can be connected to the system to warn personnel outside the treatment room that the laser is in operation.

Installation instructions are provided in Chapter 6-3
Recommendations for the room installation.

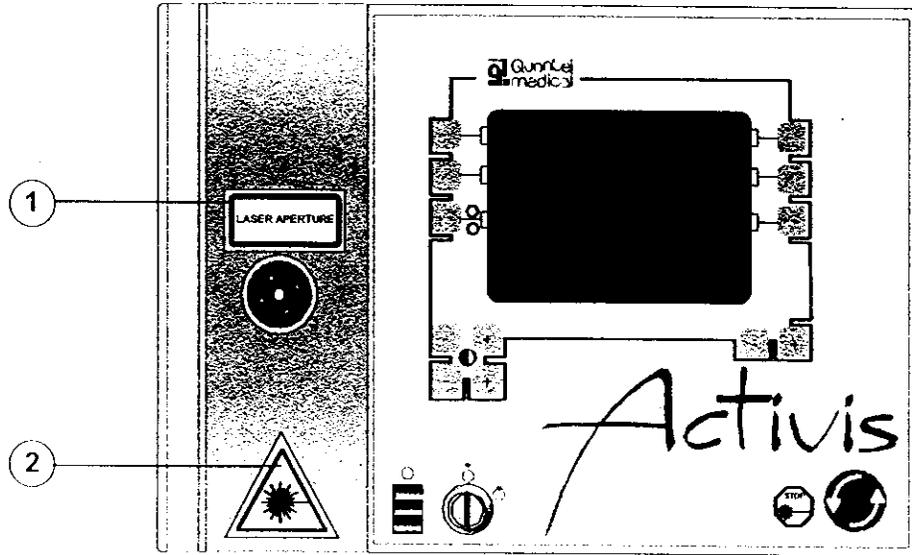
12. Never open the laser enclosure. Hazardous levels of visible and invisible optical radiation are present inside. Refer service problems to qualified personnel.
13. Regular maintenance, including calibration, should be performed by the user. This is described in **Chapter 9**. This helps assure trouble-free operation.

Always use large radius bends in the optical fiber to ensure full transmission and proper functioning.

Do not operate the system with frayed or faulty cords or fibers, or if the system appears to be malfunctioning (e.g. no sound is emitted when the pedal is depressed, the laser is sparking, smoking etc. Smoking is not permitted in the treatment area). If the laser malfunctions, shut it down, remove the key, unplug it and post a sign stating that the machine is out of order. Contact your Quantel representative for repairs.

5 - LABEL PLACEMENT DIAGRAM

5-1 STICKERS ON THE FRONT PANEL



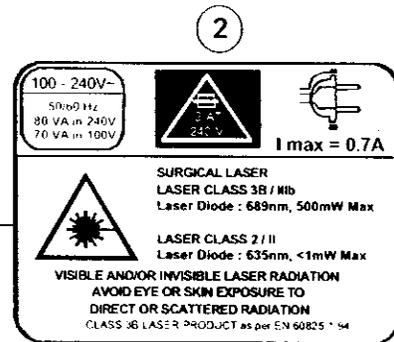
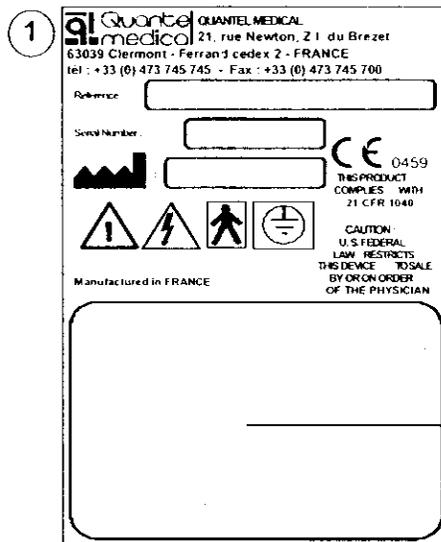
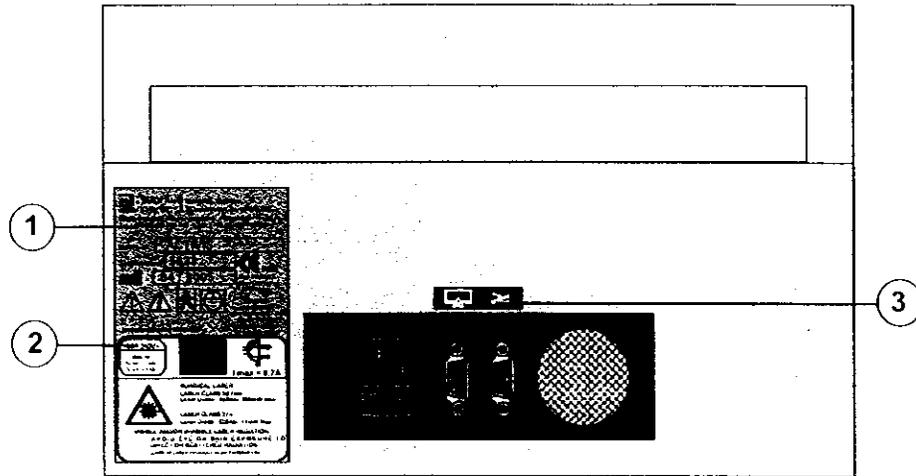
1 The Laser aperture is at the end of fiberoptic, located next to the laser aperture on the front of the unit.



2 Attention label. This label requires the user to consult the users guide before continuing on with any additional operation and/or function of the device. It is located near the laser aperture.

5 - LABEL PLACEMENT DIAGRAM

5-2 STICKERS ON THE REAR PANEL



"BF" Symbol

"Classe 1": Accessible conductive parts are connected to Ground

"Type BF": Protection against electrical shocks.

The applied parts should be isolated from the ground.

IP 20: Normal device.

3

Remote plug
connector



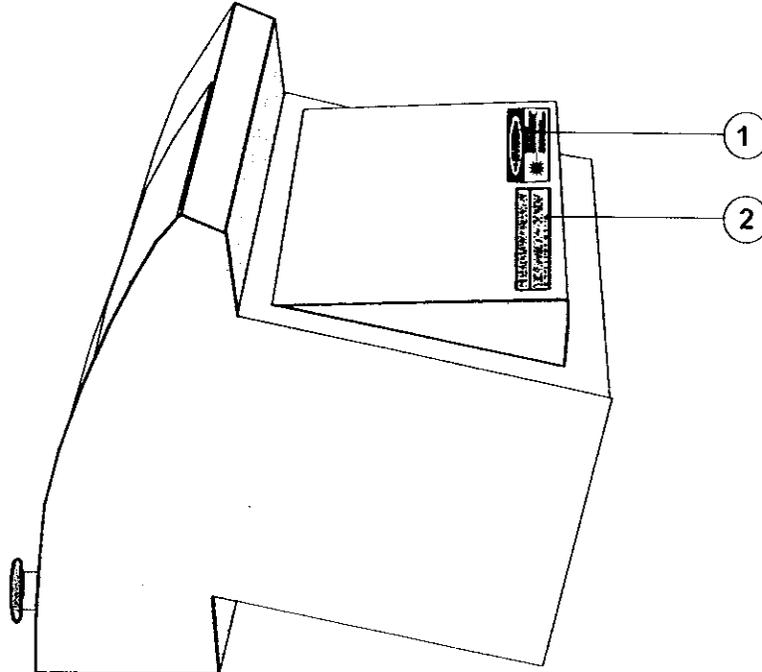
Footswitch
connector



689 nm laser

5 - LABEL PLACEMENT DIAGRAM

5-3 STICKERS ON THE COVER



①

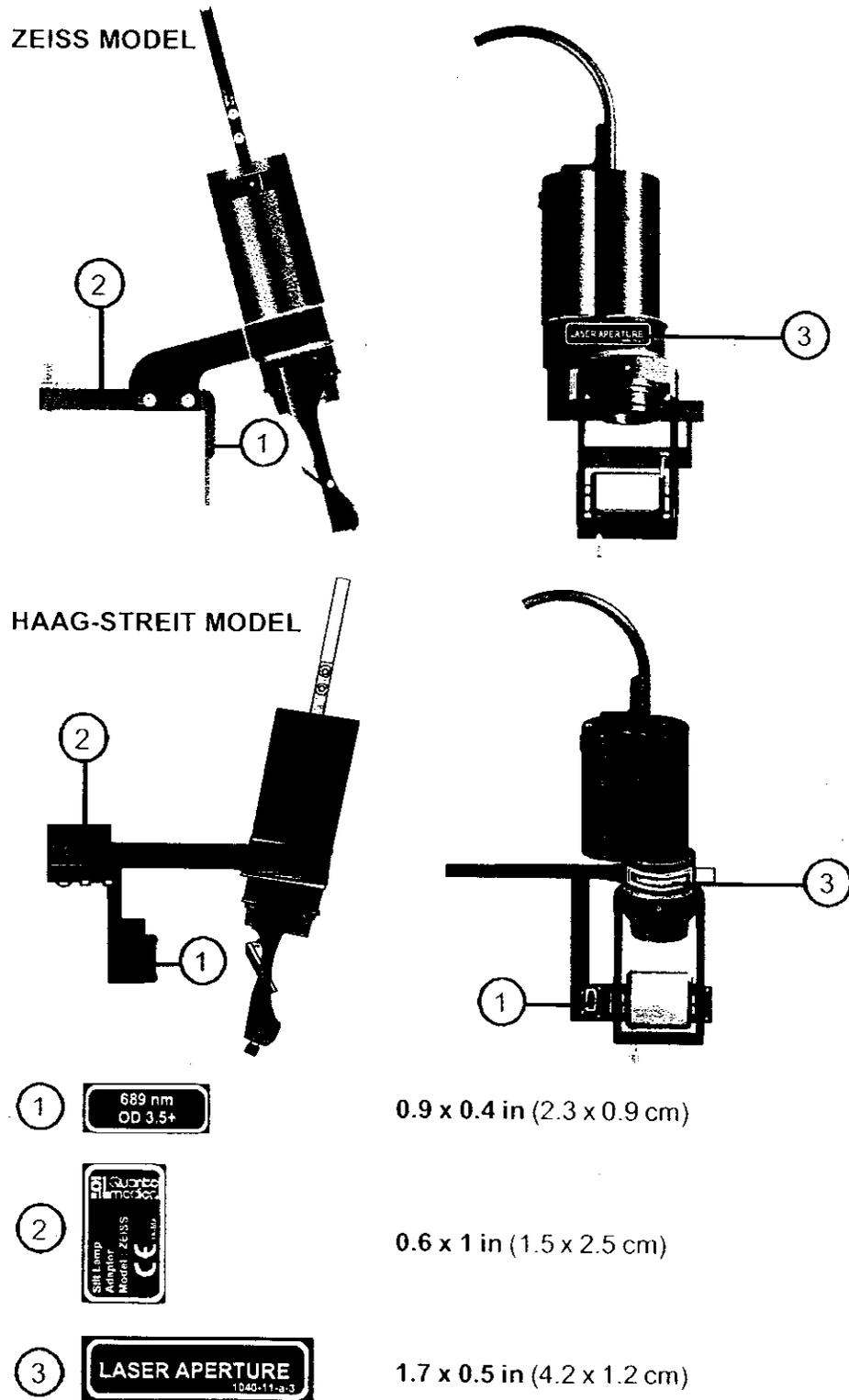
DANGER	
	LASER RADIATION Avoid eye or skin exposure to direct or scattered radiation
	Diode 689 nm 500 mW CLASS IIIb LASER PRODUCT

②

CAUTION : FEDERAL US LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN OR AN OPTOMETRIST LICENCED BY THE LAW OF THE STATE IN WHICH HE PRACTISES TO USE OR ORDER THE USE OF THIS DEVICE.
DANGER : EXPLOSION HAZARD DO NOT USE IN PRESENCE OF FLAMMABLE ANESTETICS OR IN OXYGEN-RICH ATMOSPHERE CAUTION : ELECTRIC SHOCK HAZARD DO NOT OPEN REFER SERVICING TO QUALIFIED SERVICE PERSONNEL

5 - LABEL PLACEMENT DIAGRAM

5-4 STICKERS ON THE PDT ADAPTOR



6 - INSTALLATION

6-1 PACKING LIST

Before assembling the system, make sure the package contains all components ordered.

Below is a list of the components included with the basic console.

- Laser console
- Footswitch
- Power cord
- User manual (XL ACTI ME US)
- Keys
- Slit lamp adaptor (with the fiber optic and power connection)
- Protection goggles

6-2 UNPACKING

Prior to shipping, this instrument was packed with special care in order to minimize transport risks.

However, before unpacking your laser, check the packaging for signs of damage or improper handling. If you discover any, contact the shipping company immediately and only remove the packaging in the presence of a representative of the company. Draw up a list of all damaged parts and make sure it is signed by the transport company's representative.

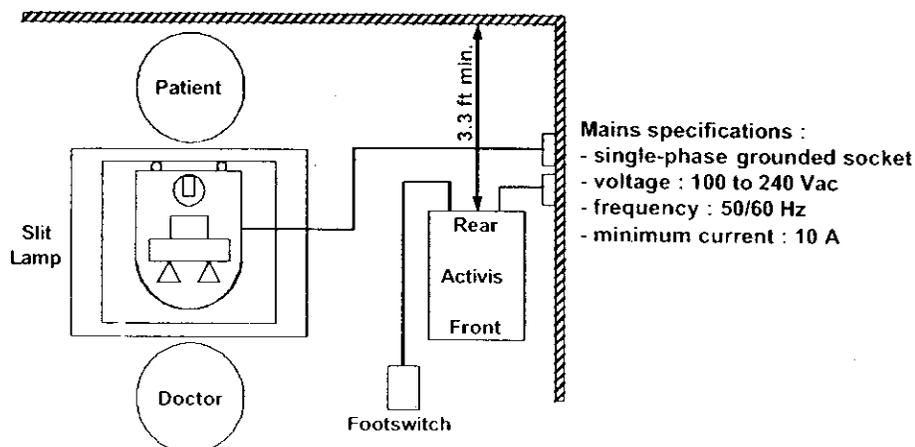


WARNING: if the instrument is at a temperature less than **50°F / 10°C**, switching on the instrument may cause serious damage. Unpack the instrument and leave it at normal temperature for at least **half a day** to ensure that the internal components warm up gradually.

6-3 RECOMMENDATIONS FOR THE ROOM INSTALLATION

6-3-1 LOCATION

- The instrument should be positioned in such a way that the laser beam cross out of the slit lamp cannot be directed towards an opening (e.g. door or window.) or reflecting material.



- The instrument must be installed in a dust free room; carpeted walls or floors should be avoided.
- When not in use, the system should be covered to prevent dust settling onto the optics.
- Ensure that the fan vents on the machine are not blocked or obstructed.

6-3-2 ELECTRICAL REQUIREMENTS

2 grounded sockets with single phase:

- Voltage: 100 to 240 Vac
- Frequency: 50 / 60 Hz.
- The plugs must be able to deliver a minimum current of 10 A.



WARNING: Use two different sockets for the Laser and slit lamp main connections.

Ensure that the socket is properly grounded.



WARNING: Do not use a 3-prong adapter to accommodate an ungrounded 2-prong wall receptacle.

6 - INSTALLATION

6-3-3 DOORSWITCH INSTALLATION

In order for the laser to fire, the built-in interlock circuitry must be closed via the serial port on the rear panel, either by a doorswitch circuit, or by the dummy REMOTE connector plug that comes with the laser.

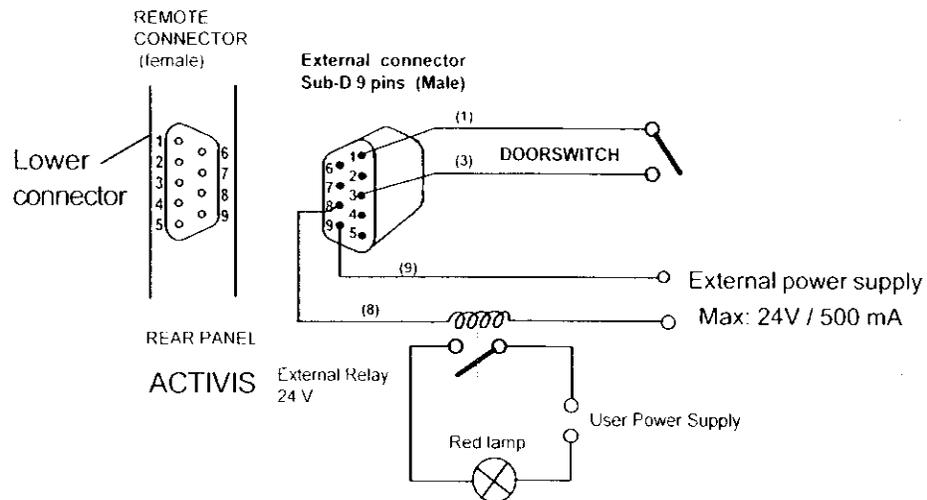
(The user must provide either a magnetically or mechanically actuated doorswitch). The switch contacts within the circuit are either closed or opened by the door. An open circuit stops the laser operation.

The switch and its wiring must be rated for at least 24 Vac and 500 mA . The wires should be able to terminate with a standard male 9-pin "D" type connector which is commonly used for computer serial port connections.

One wire should terminate on pin 1, the other on pin 3.

The order of polarity is not important.

Even if this option is not used, the REMOTE connector plug must be left in place in order for the system to go in Ready mode.



To connect the doorswitch to the laser system, simply the doorswitch wiring to the REMOTE connector plug on the rear panel. Once wired be sure to seat it firmly to avoid unexpected interlock of the system.

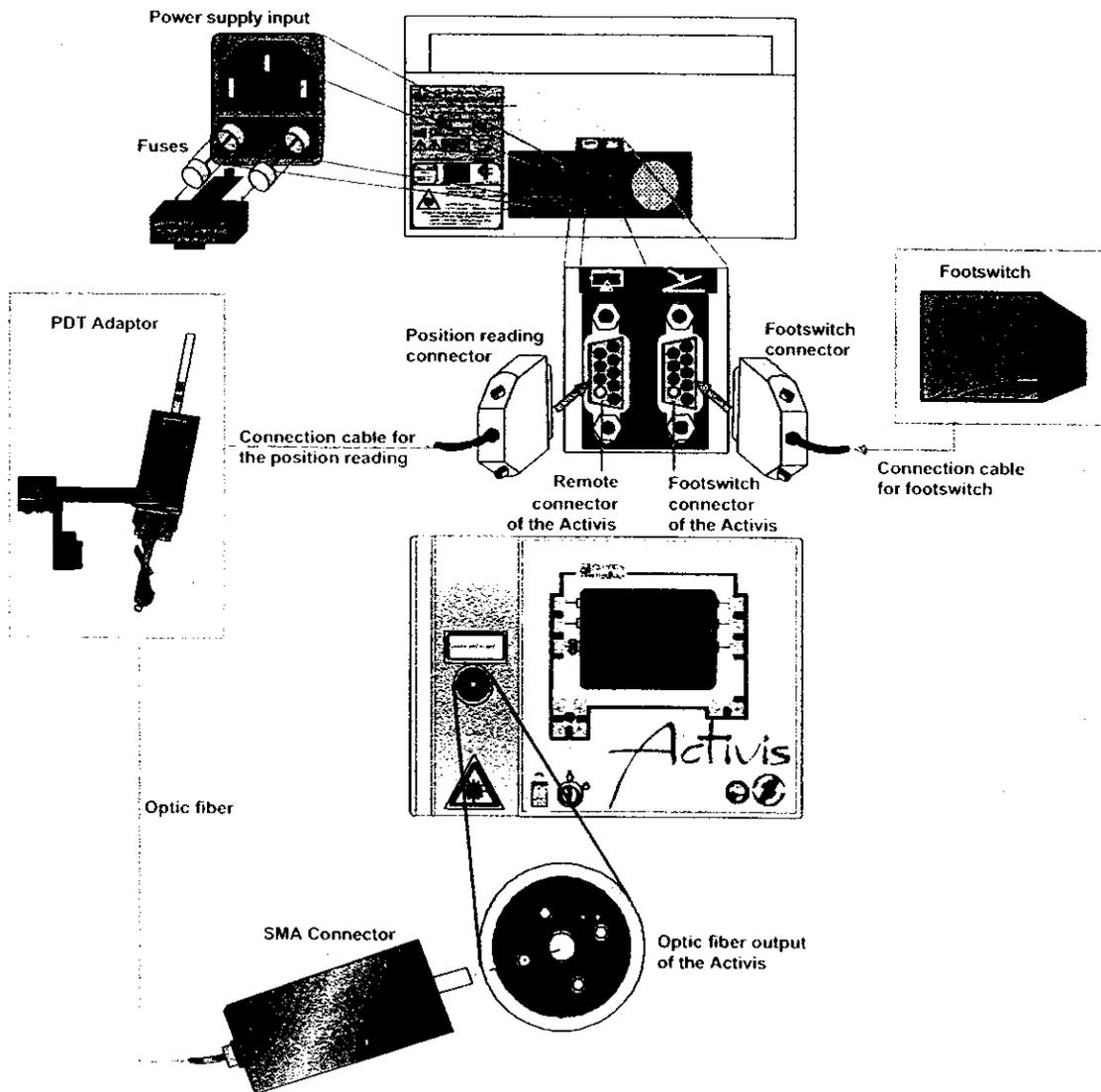
6-3-4 EXTERNAL RED LIGHT INSTALLATION

The red light must be driven via an external relay (see the figure above). To work a connection must be made between pins 8 and 9 of the same Sub-D/9 pins on the REMOTE plug to the external relay. The contacts are ON when the laser is operating

An external power supply with a maximum of 24 Vac / 500 mA must be used for external relay activation.

The red light circuit power is at the user's choice.

6-4 CONNECTION OF THE ELEMENTS

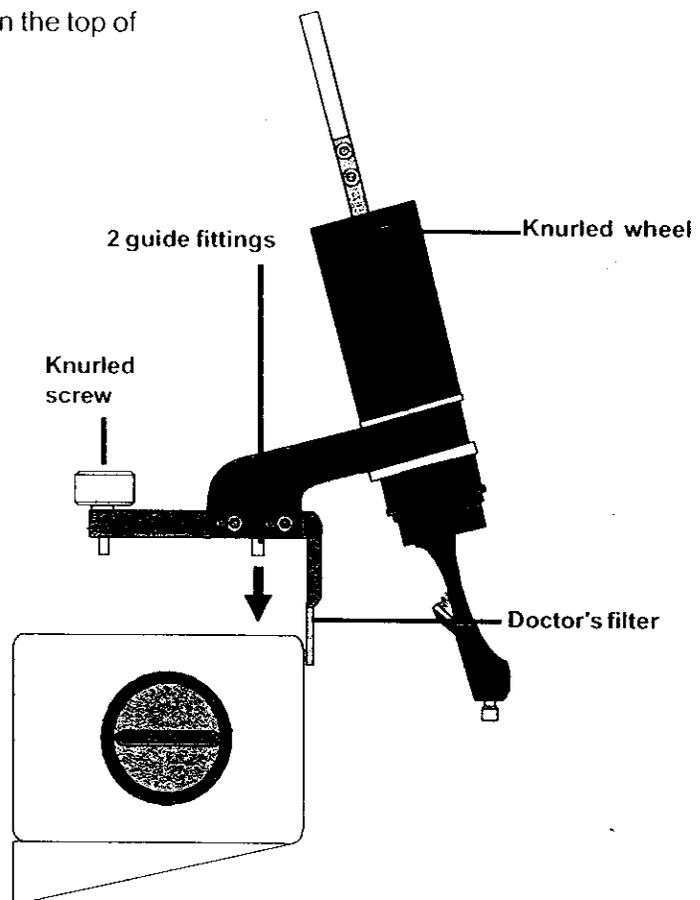


6 - INSTALLATION

6-5 INSTALLATION OF THE PDT ADAPTOR

6-5-1 ADAPTOR POSITIONING FOR ZEISS 30 OR 120 SL

- Switch off the device.
- Rotate the slit lamp projector to a side of the eyepieces.
- Mount the adaptor introducing the 2 guide fittings into the 2 corresponding holes on the top of the slit lamp.



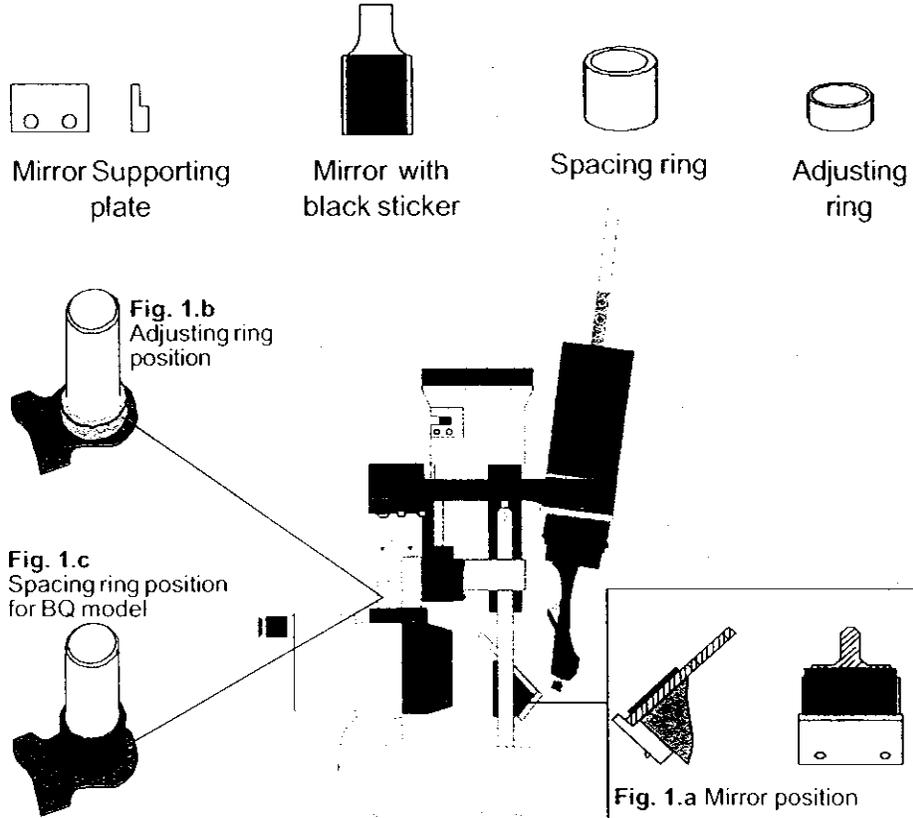
WARNING :

The doctor's filter must cover the binocular optics to prevent any risk of transmission of the laser beam through the binocular.

- Check if the slit generator can be positioned behind the semireflecting filter without touching it.
- Tighten the knurled screw.

6-5-2 ADAPTOR POSITIONING FOR HAAG STREIT 900 BM-BQ

List and position of the adaptor accessories placement.



The slit lamp illumination mirror can produce an unwanted secondary reflection of the aiming beam. Therefore a special mirror that blocks aiming beam reflection must be installed.

- Switch the device off.
- If necessary, remove the slit lamp applanation tonometer.
- Rotate the slit lamp projector to the left of the eyepieces.
- Remove the slit lamp illumination mirror, sliding it out of its holder.
- Insert the Quantel mirror supplied and slide it in until it abuts against the stop (**fig. 1.a**).
- If a more intense aiming beam is required, use the adjusting ring, placing it on the tonometer support (**fig. 1.b**).
- For the BQ models, place the spacing ring on the tonometer support (**fig. 1.c**). It is possible to place the adjusting ring (**fig. 1.b**) on top of the spacing ring to increase the light intensity of the red aiming beam.

The doctor's filter must cover the binocular optics to prevent any risk of transmission of the laser beam through the binocular.

- Place carefully the adaptor on the tonometer support and tighten the screw.

6 - INSTALLATION

6-5-3 CONNECT THE ADAPTOR TO THE LASER SYSTEM

- Switch the Activis off.
- On the back panel of the laser system, ensure that the footswitch and door interlock are properly connected (see § 6-3 and 6-4).
- Remove the dust caps from the laser fiber optic connector and the laser console aperture. Insert the laser fiber optic connector into the laser console aperture. Rotate the threaded connector clockwise until finger-tight to secure the connection. Do not over-tighten. The connector must be fully seated on the receptacle. If it is not, the laser cannot be enabled. Plug in the adaptor power supply into the back panel receptacle.
- Ensure that the proximal and distal ends of the optical fiber have large bend radiuses. A sharp bend in the optical fiber can cause optical transmission loss resulting in reduced laser power.

6-5-4 ADJUSTING OF THE ADAPTOR

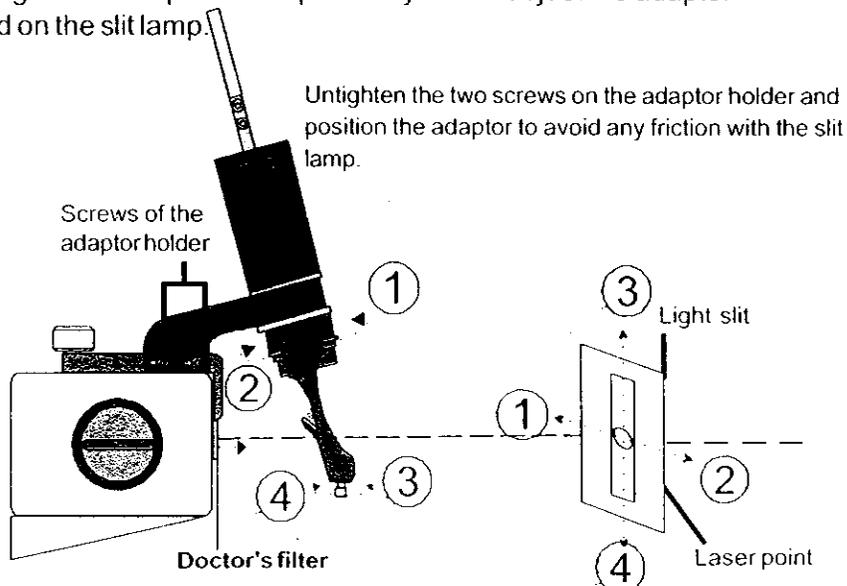
6-5-4-1 ZEISS 30& 120 SL ADAPTOR ADJUSTMENT

Spot location adjustment:

The spot location has to be adjusted to place it in the center of the illumination slit.

The adaptor has two axis of rotation for adjustment (see below).

However if the amplitude of rotation is not enough to adjust the spot to the desired location or if the adaptor rubs against the slit lamp when swinging the slit lamp to a new position you can adjust the adaptor forward on the slit lamp.



6-5-4-2 HAAG-STREIT 900 BM-BQ ADAPTOR ADJUSTMENT

- Doctor's filter position:

Unscrew the 2 screws of the filter support and slide the filter forward or backward to adjust precisely the filter position.

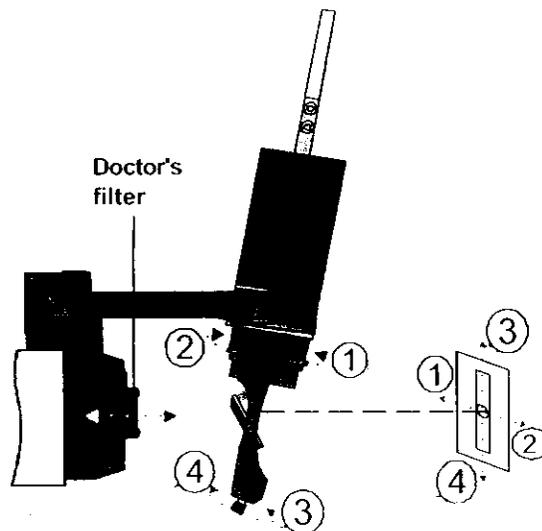
When properly adjusted the adaptor easily fits on the binocular and the filter does not prevent the rotation of the slit generator.

Spot location adjustment:

The spot location has to be adjusted to place it in the center of the illumination slit.

The adaptor has two axis of rotation for adjustment (see below).

However if the amplitude of rotation is not enough to adjust the spot to the desired location or if the adaptor rubs against the slit lamp when swinging the slit lamp to a new position you can adjust the adaptor forward on the slit lamp.



After a correct installation, there should not be any friction between the adaptor and the slit lamp.



WARNING :

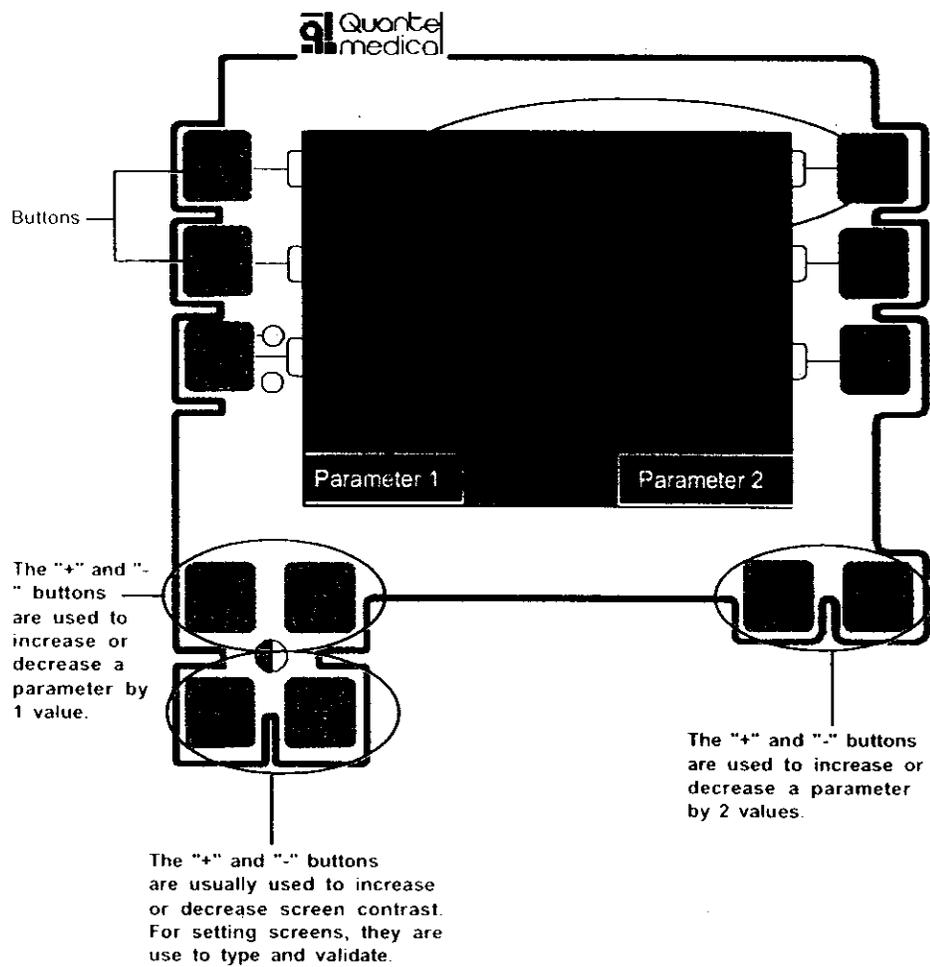
The doctor's filter must cover the binocular optics to prevent any risk of transmission of the laser beam through the binocular.

7 - CONTROL PANEL

PRINCIPLE:

On each screen, the buttons have different functions.
These functions are clearly displayed in front of each button on the Liquid crystal display.

The buttons are used to scroll the different function possibilities.



8-1 CONTROL PANEL AND SAFETY

The LCD screen of the front panel displays different screens depending on the state of the unit.

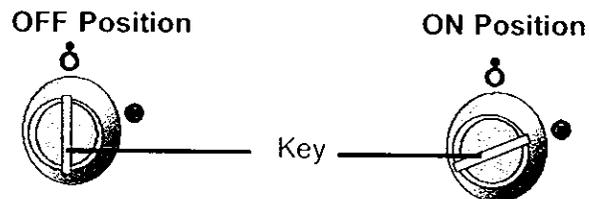
The first screen displayed when the unit is turned ON (before the KEY CONTROL is ON) is shown in chapter " 8-2 Turning ON the unit ".

The control panel showing all laser parameters is displayed only when the Laser is ON (See § 8-4).

SAFETY CONTROLS:

The laser system as has an interlock system that allows the laser to be ON only after the delivery system is connected correctly. Connections enables the laser startup by the key control.

KEYSWITCH (ON / OFF)



When activating the main switch of the unit, if the key is switched to:

- "ON", the message is: "Turn the key to OFF" is displayed,
- "OFF", the message, "Turn the key to 'ON' to turn the Laser ON " is displayed on LCD screen.

See chapter " 8-2 Turning ON the unit ".

NOTE : The key cannot be removed when the laser is activated.
Turn the key to the "OFF" position to turn the laser OFF.

STOP

The large red STOP button will instantly stop all laser functions when pressed.



IMPORTANT: This panic button must **ONLY** be used in emergencies.

To restart the system after using the panic button:

- 1 - twist the button clockwise and allow it to pop back up,
- 2 - turn the keyswitch OFF ('OFF' position),
- 3 - then restart the system normally.

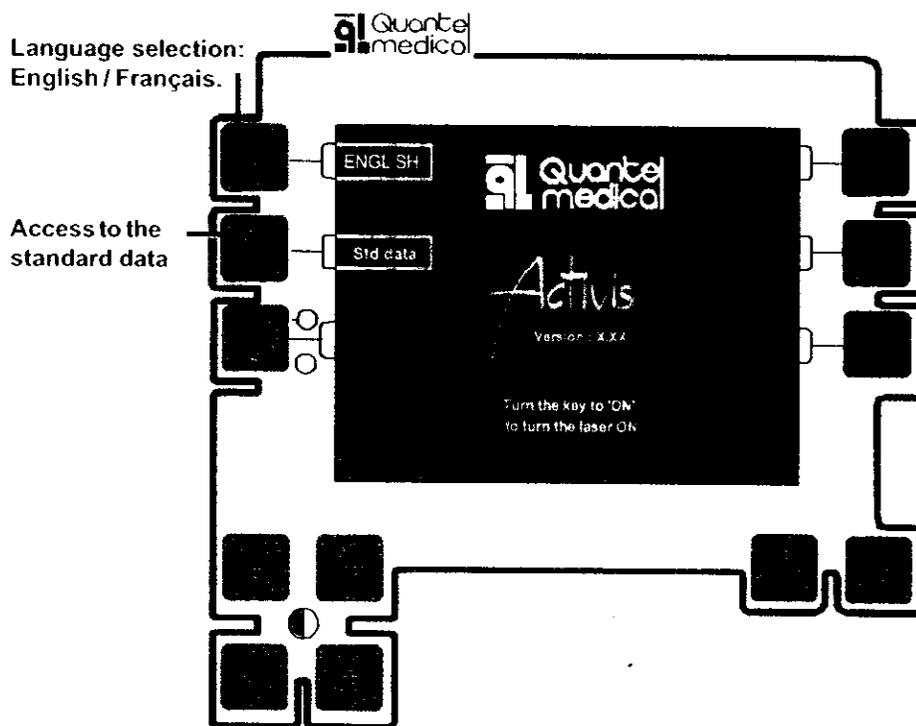
Timing and power settings will return to their default values.

8 - OPERATING PROCEDURES

8-2 TURNING THE UNIT ON

- Make sure the main power cable is connected.
- Check the panic button. If it is depressed, pull it out, turning clockwise.
- Activate the master switch at the front of the unit. A beep will sound.

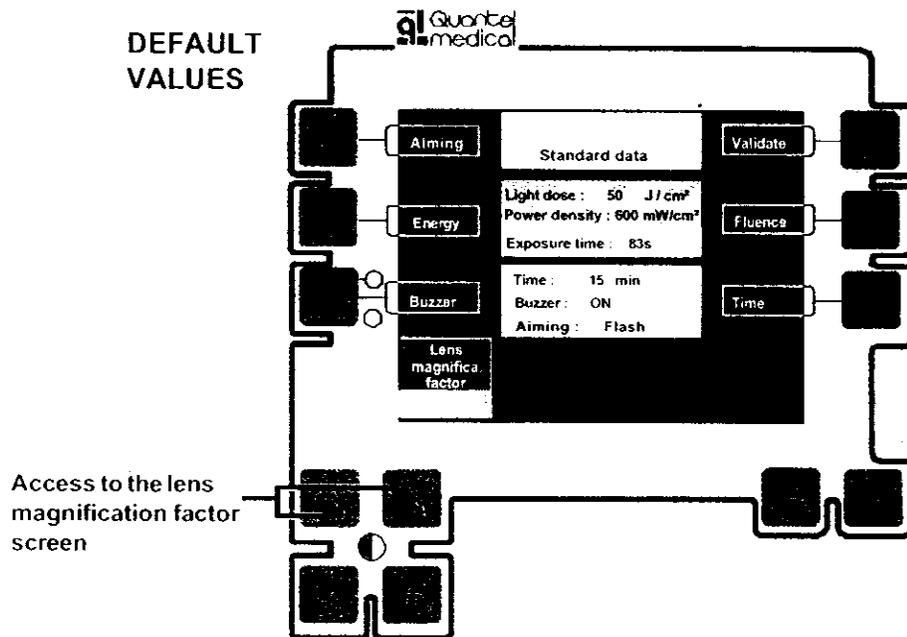
If the key is in the "OFF" position, the following message will appear:



Conditions	Messages
TURNING ON THE UNIT: If the key is "ON"..... If the key is on "OFF".....	Turn the key to "OFF" Turn the key to "ON" to turn the laser ON
TO START THE LASER: Key in position "ON".....	Please Wait
IF THE LASER IS NOT USED: After 10 min. in Stand-by	Automatic laser turn OFF Turn the key to "OFF"

8-3 STANDARD DATA FOR TREATMENT PARAMETERS

On this screen, you can store your standard data. These parameters stay in the Activis memory, even when the laser is turned Off. Selecting the "Std data" button from the display shown on the previous page produces the screen below.



8-3-1 AIMING BEAM

This function allows you to choose between a continuous or pulsed aiming beam. The function can also be toggled from any screen by pressing both the lower "+" and "-" buttons.

8-3-2 ENERGY

This Selects the energy density used, from 50 to 800 mW/cm². Hold down the button to scroll through to the desired setting.

8-3-3 BUZZER

The buzzer signal emitted during the last 15 seconds of the infusion time countdown can be activated or deactivated (see section 8-3-5).

8-3-4 FLUENCE

This selects the required light dose from 5 to 95 J/cm².

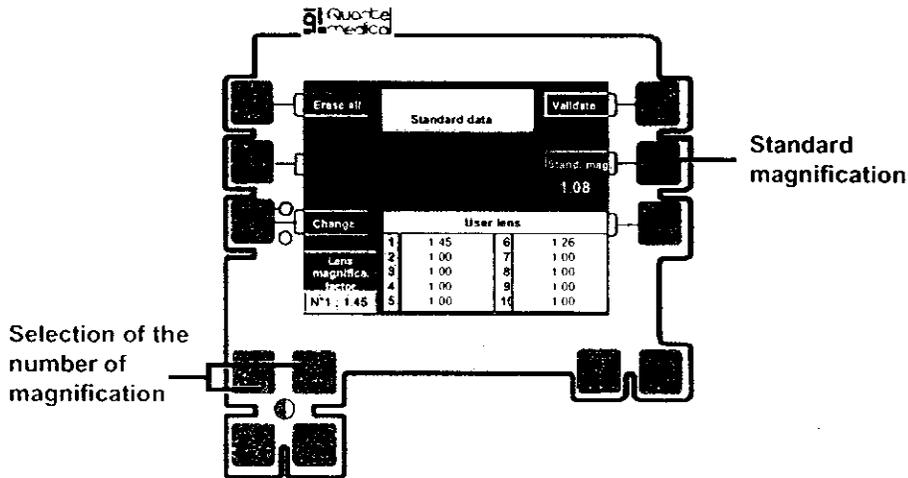
8-3-5 TIME (COUNTDOWN TIMER)

This selects the time desired (5 to 20 min.) to elapse from photosensitizer infusion start to the Laser treatment start (15 min. according to the Visudyne® labeling). This time allows the drug to accumulate in the CNV area. A buzzer sounds during the last 15 seconds of the countdown.

8 - OPERATING PROCEDURES

8-3-6 LENS MAGNIFICATION FACTOR

Pressing one of the two "+" or "-" buttons of the "Lens magnification factor" (see previous page), will display the following screen:



A table of 10 magnification values of your personal lenses can be stored.

Select the desired magnification number to set (1 to 10) with "+" and "-" buttons, and press the "Change" button.

The standard magnification value can also be changed, by pressing the 'Stand. mag' button and entering a value on the screen as described below. Press the 'Validate' button to input the value into memory.

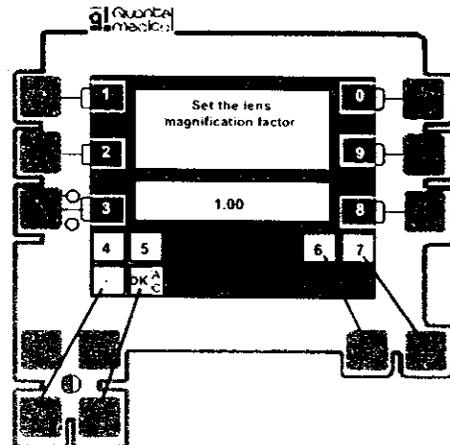
Those values will be added to the following preset list in the Activis: 1.04 , 1.05 , 1.08 , 1.25 , 1.44 , 1.47 , 1.50 , 1.60 , 1.75 , 1.90 , 2.01 (see chapter 8-5-3).

Enter a value on setting screen :

Each button on screen corresponds to the numeral displayed in front of it.

The lower "-" button corresponds to the comma.

The lower "+" button enters the typed value, or erases the value if the pressure is maintained (over 2 seconds).



The range of settings is from 0.5 to 2.5x. An out-of-range value will not be accepted by the Activis.

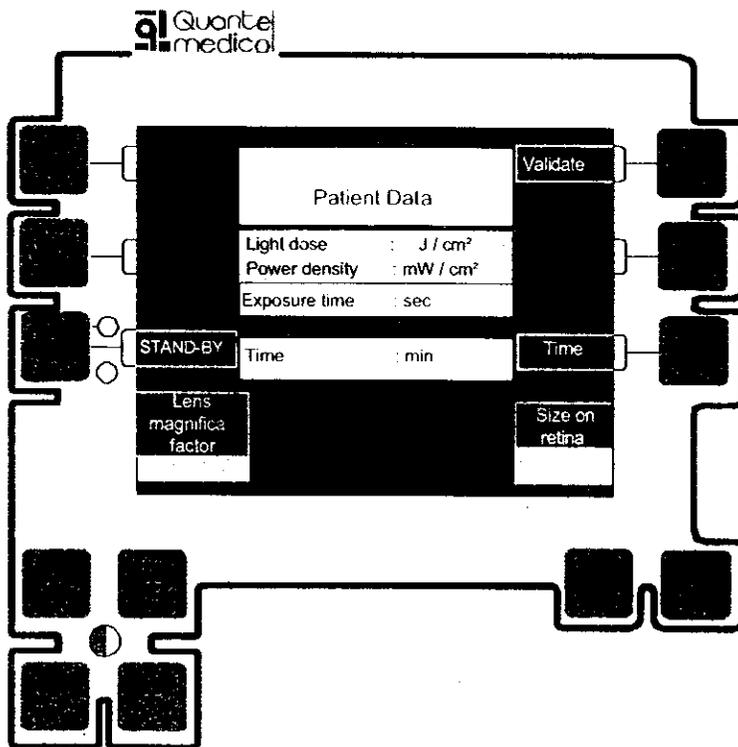
8 - OPERATING PROCEDURES

8-4 STARTING-UP THE LASER

A compatible QUANTEL MEDICAL delivery system shall always be connected to the laser console before the laser is energized. Before connecting the delivery system as instructed in the next section, the following operation sequence is required:

- 1- Insert the key in the key switch and rotate to "ON". A system self-test begins as indicated by the continuous illumination of the test indicator.

- 2- After approximately 20 seconds, the treatment laser radiation parameters are accessible via the screen shown below.



When the self-test is complete, the system will be in the standby mode as indicated on the screen.



689 nm laser

8 - OPERATING PROCEDURES

8-4-1 LENS MAGNIFICATION FACTOR

Using "+" and "-" buttons, one can select a magnification by scrolling through the stored list of values, which include the 11 ACTIVIS preset values, plus the personal list that was input in the standard screen (displayed from N°1 to N°10) plus the standard value set in the standard data screen (under "Std Mag").

Stored list:

Example :

1.04	1.05	1.08	1.25	1.44	1.47	1.50	1.60	1.75	1.90	2.01
------	------	------	------	------	------	------	------	------	------	------

Personal list:

+

N°1: 1.06	N°2: 1.16	N°8: 1.30	N°5: 1.55	N°9: 1.80
-----------	-----------	-----------	-----------	-----------

Standard value:

+

Std: 1.10

Thus a total of 22 magnification values can be scrolled in this screen.

8-4-2 TIME (COUNTDOWN TIMER)

Select the time desired (5 to 20 min.) to elapse the photosensitizer infusion start the laser treatment start (15 min. according to the Visudyne® labeling). This time allows the drug to accumulate in the CNV area. A buzzer sounds during the last 15 seconds of the countdown.

8-4-3 SIZE ON RETINA

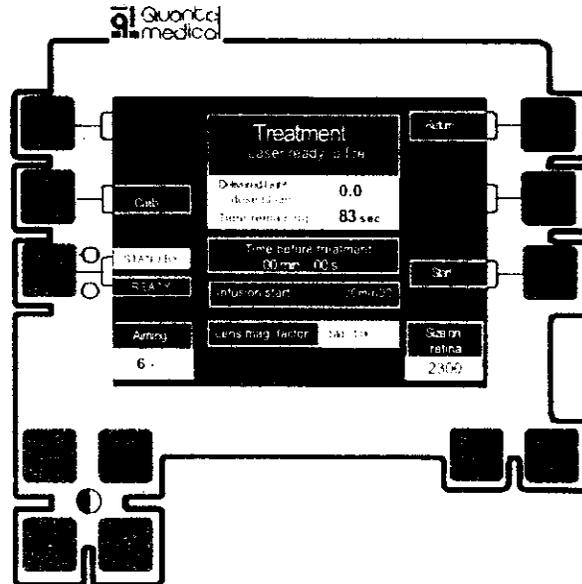
Select the required spot size by turning the knurled wheel on the adaptor.

The range is from 1000 to 5400 µm without magnification, and up to 8000 µm with 1.5 magnification.

NOTE: The size displayed on the screen is the size of the spot on the retina after magnification. See chapter 8-6 for further information.

8-5 OPERATING MODE

When all the parameters have been selected, press the Validate button to enter the values. The screen below appears showing the entered treatment parameters.



8-5-1 SIZE ON RETINA

To change the spot size of the treatment beam, turn the knurled wheel on the adaptor. The size displays as shown on the above screen. See chapter 8-6 for further information.

NOTE: If the size is out-of the allowed range, the size field displays a dash character ("-") and the message "Waiting size" appears. The laser will not fire in this state.

8-5-2 AIMING BEAM

The red aiming beam of the diode laser has a maximum power of 0.9 milliwatts in the highest setting (12). Use the "+" and "-" buttons to increase or decrease the aiming intensity from 0 to 12. Press both buttons to have a pulsed beam (*) or a continuous beam (-). To switch OFF the aiming beam set it to 0 by pressing "-" button. To switch ON aiming beam again, press the "+" button.

NOTE: Turning the aiming beam OFF switches the treatment laser to the stand-by mode. **The treatment beam cannot be delivered when aiming beam is turned OFF.**

8 - OPERATING PROCEDURES

8-5-3 CALIB.

This button is used to access the calibration menu (see Appendix 1) by pressing it for more than 2 seconds.

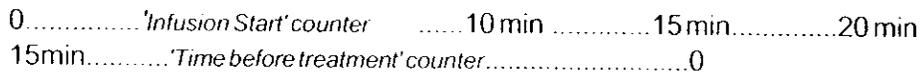
8-5-4 START (TIMERS)

Infusion start is an unlimited elapsed timer. It is a reliable time reference for the sequence of treatment procedures.

'Time before treatment' is a countdown timer, whose value is set on the previous screen.

Press the START button simultaneously with the infusion start to activate the "Infusion Start" elapsed timer and "Time before treatment" countdown timer.

With Visudyne for example, the infusion is for 10 min ; subsequent laser treatment should occur 15 to 20 min after the infusion start.



A buzzer signal is emitted during the last 5 minutes of the 'Time before treatment' countdown. It sounds every second for the last 15 seconds. To reset the timers (elapsed and countdown), press the Start button for more than 2 seconds. **All timers are reset.**

8-5-5 RETURN

This button will allow you to return to the previous screen in order to change parameters between two patients or change other parameters.

8-5-6 LASER STANDBY / READY

The button enables or disables the firing of the treatment beam.

The laser is in Standby: Green LED ON

The laser is Ready to fire: Yellow LED ON

You are now ready to treat the patient, see chapter 8-7 for information on the Operating Procedure.

8-6 SPOT SIZE

8-6-1 SPOT SIZE AND POWER DENSITY

The spot size of the treatment beam is controlled by the knurled wheel on the PDT adaptor. When the required spot size is selected, the spot size is immediately displayed on the control screen in "size on retina" field.

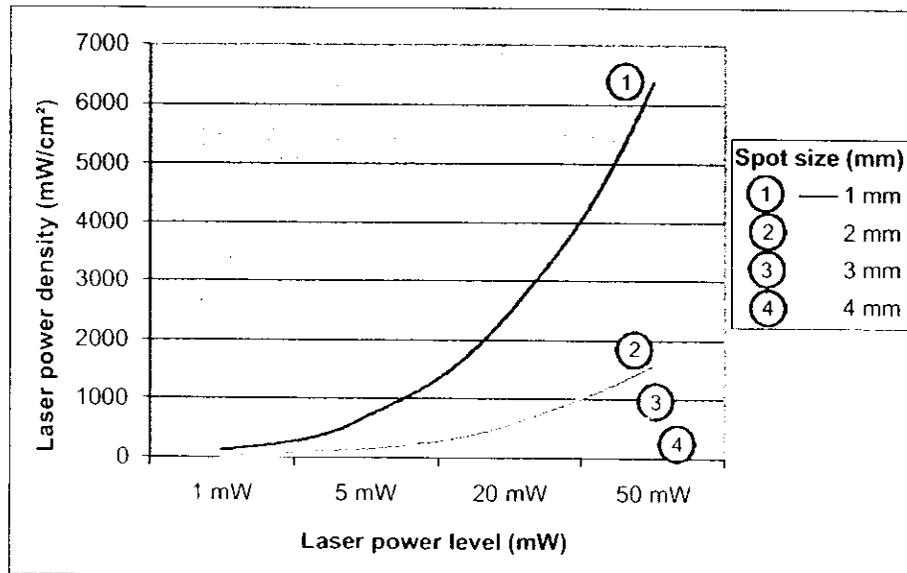
8-6-2 SPOT SIZE AND POWER DENSITY

Power density at the treatment site largely determines the degree of interaction of the laser beam with tissue. Power density is defined as laser power divided by the area of the spot size. Power density can be increased by increasing the laser power or by decreasing the spot size.



CAUTION :

The relationship between spot size and power density is non linear (see graph below). For a given amount of laser power, reducing the spot size by 50% will quadruple the power density. The laser clinician must understand the relationships between spot size, laser power, power density, thermal interaction, and photochemical interaction of the laser beam with living tissue before using the laser system and the delivery system. The ACTIVIS system will automatically calculate the energy dose to be delivered to the retina, based on the spot size and power density values that are input. Therefore, for safe and effective use it is imperative that the input treatment parameter values are correct, (e.g. magnification values match the lens), and that the spot size is only as large as is necessary.



Laser power density diagram



689 nm laser

8 - OPERATING PROCEDURES

8-7 GENERAL OPERATION

- Position the patient, laser system, and the delivery system.
- Target the aiming beam on the desired treatment site.
- Fixate the patient's eye and position the aiming beam on the zone to be treated.
Select the required aiming beam intensity.
At this point check that the spot is in focus.
- When the countdown timer reaches the last 15 seconds, a beep sounds every second.
- In the Operating mode (§ 8-5), press the "READY" Mode button to enable firing. The Yellow light goes ON.
- Depress the footswitch to deliver the treatment beam to the tissue.

Keep the footswitch depressed during the entire exposure time. When the full energy dose (calculated by the ACTIVIS using treatment parameters) has been delivered, the treatment beam will stop.

If you want to stop the treatment, release the footswitch. If treatment is paused by releasing the footswitch before the exposure time limit is reached, the exposure can be resumed by depressing the footswitch again. The treatment time counter will continue to increment from the last value until the full dose is reached.

Keep the laser on standby between treatment sessions.

At the end of the treatment, press the STAND-BY Mode button. The green light will go ON. In this state the footswitch is not active.

8-8 SHUTDOWN

- 1- Turn the key switch to position "OFF" to turn the laser OFF.
- 2- Remove the key.
- 3- Switch OFF the unit with the master switch on the front panel.
- 4- If the delivery system is disconnected, be sure to put the cap back on the optical fiber output to prevent dust from collecting.



IMPORTANT: The panic switch must be used only in emergencies. It is located on front of the laser console. After use, it must be twisted and pulled out to allow the laser to function again.

9-1 LASER CONSOLE



WARNING: Disconnect AC power before cleaning the case.

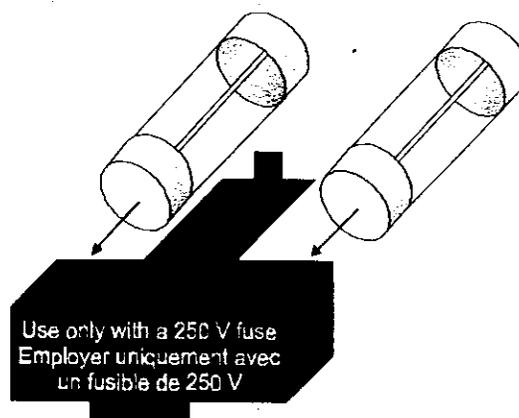
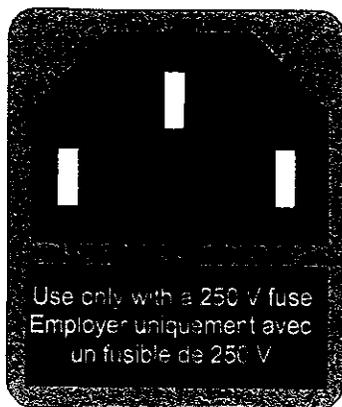
- a. The unit is ventilated via the vents at the back of the laser console.
Any dust build up should be cleaned as necessary.
Use a dry cloth to remove dust from these surfaces.
- b. The laser console is constructed from an ABS plastic material.
This part is coated with an epoxy paint.
Use only a damp cloth for cleaning. Do not use either solvents or alcohol.

All surfaces should be thoroughly dried after cleaning.

9-2 FUSE REPLACEMENT

- Switch off the device and disconnect the power cord.

Spécifications: glass fuse
2 AT - 250 V
6 x 32 mm





689 nm laser

10 - ERROR MESSAGES

LIST OF ERROR MESSAGES AND POSSIBLE SOLUTIONS

Message	Explanation and solutions
Remote interlock	The remote is open or is not properly closed safety (External door or other device). - Close the remote interlock (door etc.). Check the electrical connection of the slit lamp adaptor (at the back of the unit), near the power cord).
The pedal is pressed	The footswitch is pressed during the "Warming up" or in the "Key to Off" states: - Release the footswitch. It could be a short-circuit. - Disconnect the footswitch and see if the message disappears.
Too much humidity	Excessive humidity may cause the laser cavity to malfunction. If the laser has been cooled, condensation may raise humidity unacceptably. - let the system warm up for 3 hours at ambient room temperature.
Cavity temperature out of tolerance	The cavity temperature is too high or too low. - The instrument must be only used within the advocated temperature range: 59°F to 86°F (15°C to 30°C) After intensive use ACTIVIS may overheat. - Let it cool down for a few minutes.
Waiting size	- The position of the knurled wheel of the adaptor is out of the range. Turn it to set the into the range (see § 8-4-3) - Check that the slit lamp adaptor is connected.
Terminal	The slit lamp adaptor is not correctly connected. - Verify the connection.

10 - ERROR MESSAGES

Message	Explanation and solutions
Non calibrated terminal Call for SERVICE	- The Delivery system is not calibrated : - It must be done by authorized person only : CALL FOR SERVICE.
Hard: P< (-20%) 689	The measured power is too LOW (-20% expected). - Call for Service.
Hard: P>(+20%) 689	The measured power is too HIGH (+20 % expected). - Call for Service.
Hard: 24V < (-20 %)	The measured +24V voltage is too LOW (-20 % expected). - Call for Service.
Hard: 24V > (+20 %)	The measured +24V voltage is too HIGH (+20 % expected). - Call for Service.
Hard: Security 689	The External cell detects a 689 nm laser beam whereas it should not be. - Call for Service.
Soft: Pow. Out \pm 20%	The measured shot power fluctuates more than \pm 20% the expected value. - Call for Service.



689 nm laser

11 - OPTIONS & ACCESSORIES

To order the following systems, contact Quantel Medical or your local distributor.

11-1 DELIVERY SYSTEM OPTIONS: LIST & CODES

Delivery system options for ACTIVIS laser photoactivator 689 nm QUANTEL MEDICAL ordering codes	
Slit lamp adaptor	
Adaptor for 900 - BM/BQ HAAG-STREIT	HSBMBQ ACT
Adaptor for 30SL ZEISS	ZSL30 ACT
Adaptor for 120SL ZEISS	ZSL120 ACT

11-2 ACCESSORIES: LIST & CODES

Accessories for ACTIVIS laser photoactivator 689 nm QUANTEL MEDICAL ordering codes	
For ancillary personnel protection:	
Laser safety goggles for 689 nm	XL689PROT
For calibration purposes:	
Laser power measurement system	XLAAAWATTMETRE

11-3 CONTACT LENS MAGNIFICATION

LENS NAME		LASER SPOT MAGNIFICATION
OCULAR MAINSTER WIDE FIELD		1,5
REICHEL-MAINSTER 1X RETINA		1,05
PDT 1.6X		1,6
REICHEL-MAINSTER 2X		2
MAINSTER (STANDARD) FOCAL/GRID		1,05
MAINSTER HIGH MAGNIFICATION		0,8
THREE MIRROR UNIVERSAL		1,08
FUNDUS		1,08
VOLK	AREA CENTRALIS	0,94
	QUADRASPHERIC	1,97
	SUPERQUAD 160	2
	PDT LASER LENS	1,5
	TRANSEQUATOR	1,44
	3 MIRROR (no flange)	0,94



12 - PROFESSIONAL CLINICAL INFORMATION

The use of the Activis Laser for PhotoDynamic Therapy purposes requires complete knowledge of the Visudyne® photosensitizer. Refer to the Novartis Product Labeling for Visudyne.

INTENDED USAGE:

The Activis™ Laser system and the ZSL30 ACT™, ZSL120 ACT™, and HSBMBQ ACT™ Slit Lamp Adaptors are intended to be a light source for the photoactivation of the light activated drug Visudyne® (Verteporfin for injection) in photodynamic therapy for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration, pathologic myopia or presumed ocular histoplasmosis.

CONTRAINDICATIONS:

Relative to Visudyne®: Visudyne (Verteporfin for injection) is contraindicated for patients with porphyria or a known hypersensitivity to any component of lipid-based formulation.

Relative to Laser: Patients with following symptoms which prevent visualisation of target tissue are contraindicated for Laser treatment:
- cloudy cornea or extreme haze of the aqueous humor or the anterior chamber.

SPOT SIZE DETERMINATION:

The treatment spot size should be 1000 microns larger than the greatest linear dimension of the lesion on the retina to allow a 500 microns border, ensuring full coverage of the lesion. The maximum spot size used in the clinical trials was 6400 microns.

The nasal edge of the treatment spot must be positioned at least 200 microns from the temporal edge of the optic disc, even if this will result in lack of photoactivation of CNV within 200 microns of the optic nerve.

LIGHT APPLICATION:

Initiate 689 nm wavelength laser light delivery to the patient 15 minutes after the start of the 10 minutes infusion with Visudyne®. Photoactivation of Visudyne® is controlled by the total light dose delivered. In the treatment of choroidal neovascularization, the recommended light dose is 50 J/cm² of neovascular lesion administered at an intensity of 600 mW/cm². This dose is administered over 83 seconds.

12 - PROFESSIONAL CLINICAL INFORMATION

RETREATMENT:

The physician should re-evaluate the patient every 3 months and if choroidal neovascular leakage is detected on fluorescein angiography, therapy should be repeated.

ADVERSE EFFECTS:

Adverses effects of the Activis™ lasersystems could be related to inappropriate dosages or improper use of the device that could result in incomplete treatment due to partial photoactivation of VISUDYNE, over treatment due to over-activation of VISUDYNE, or damage to suurounding normal tissue. The Adverse Events associated with VISUDYNE treatment are described in the Package insert for VISUDYNE distributed by Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936

WARNING AND PRECAUTIONS:

Following injection with Visudyne® (Verteporfin for injection), care should be taken to avoid exposure of skin or eyes to direct sunlight or bright indoor light for 5 days.

Patients who experience severe decrease of vision of 4 lines or more within 1 week after treatment should not to be retreated, at least until their vision completely recovers to pretreatment levels and the potential benefits and risks of subsequent treatment are carefully considered by the treating physician.

Following VISUDYNE treatment, patients may develop visual disturbances such as abnormal vision, vision decrease, or visual field defects that may interfere with their ability to drive or use machines. Patients should not drive or use machines as long as these symptoms persist.

Although the aiming beam is a low power laser, it is an intense light source. Retinal exposure to the aiming beam must be limited to the minimum required for target acquisition

PROTECTION FOR PERSONNEL:

When viewing the treatment area through the ZSL30 ACT™, ZSL120 ACT™, and HSBMBQ ACT™ slit lamp adapters, the operator is protected from backscattered radiation by a safety filter. Make sure the filter is in place on the adapter, and is not damage (e.g. splintered, cracked, etc.). Everyone in the treatment area should wear appropriate protective eyewear for the 689 nm wavelength. The Quantel protective goggles have an optical density of 5 for the 689 nm wavelength.

POWER CALIBRATION TEST

POWER CALIBRATION TEST

Recalibrate only when indicated by the results of the calibration test as outlined below.

Equipment Required:

Ophir Laser Joulemeter Model NOVADISPLAY, or equivalent.

Quantel Medical Code: "XL AAA WATTMETRE".

The meter should be calibrated periodically according to the manufacturer's recommendations.

Do not use Silicon Photocell type meters.

When performing calibrations, wear appropriate eye protection (689 nm goggles of L4 class).

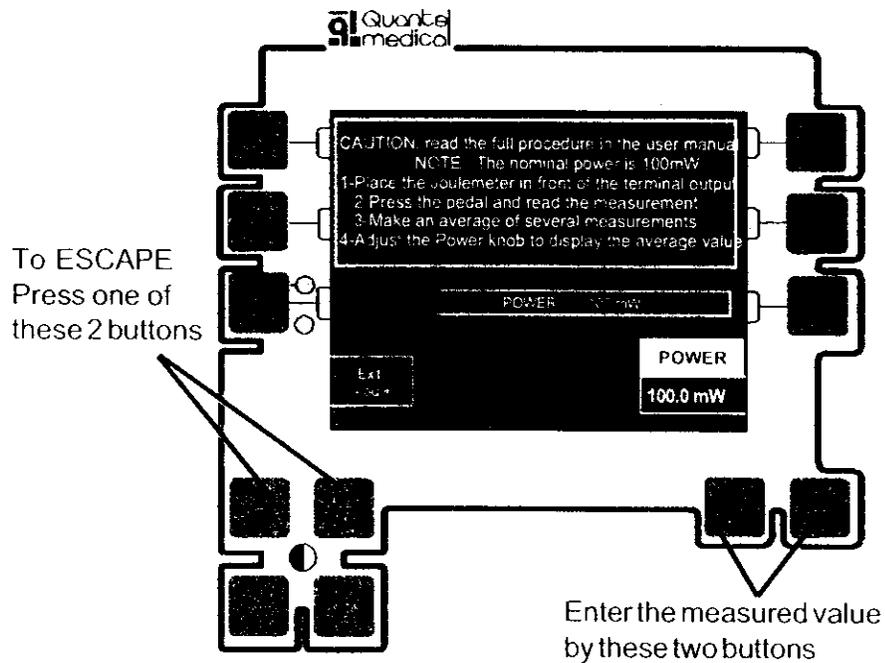
- Step 1:** Start the laser, turning the KEYSWITCH to the "ON" position.
- Step 2:** If you are using the Ophir power meter, select **0.1** second exposure duration and set the meter to operate in the "**ENERGY**" mode.
- Step 3:** Direct the adaptor aiming beam output into the photodetector of the laser power meter to obtain a **defocused aiming beam spot** occupying the largest possible part of the sensitive surface.
Always assure that the full diameter of the defocused beam is striking the active surface of the power meter's photodetector.

NOTE: A tightly focused beam may damage the photodetector.

- Step 4:** For non-Ophir power meters, set the measurement range of the meter as required by the power meter owner's manual.
- Step 5:** In the operating screen (see § 8-5), press the CALIB. function button in front during more than 3 seconds until the calibration display appears.

DELIVERY SYSTEM OUTPUT POWER CALIBRATION

The calibration is made at 100mW power and 0.10s exposure time.
 Energy = (power) x (Expos.). The Joulemeter will give the readings in mJ.
 The nominal value adjustment is limited to +/- 20%: from 80 to 120 mW.



PROCEDURE:

NOTE: To be sure of the measurement validity, the Joulemeter must have been calibrated periodically by a registered laboratory according to the manufacturer's recommendations.

- 1- Place the joulemeter in front of the laser beam, at the terminal output, so that the spot occupies the largest possible part of the sensitive surface : Do not place it at the focal distance.
- 2- Protect yourself from the laser reflexions with the 689 nm goggles (Class L4). Press the pedal to obtain the measurement.
- 3- Make an average of 10 measurements (for example): Note these values: the differences should not exceed 5%.
- 4- Calculate the average and display this value by pressing the left "+" and "-" buttons. This correction will then be applied over all the power range.
- 5- To store the NEW calibration value, ESCAPE pressing the right "+" or "-" buttons.



VENDORS

1- ANSI Z136.3 -1996

Standards for the Safe Use of Lasers in Health Care Facilities

Order from: Laser Institute of America
5151 Monroe Street
Toledo, OH 43623
U.S.A.

2- LASER SAFETY GOGGLES FOR 689NM

(Ref (EN 207): DIR 676-842 L4)

Retailer:
Noir Laser Company, L.L.C
P.O. Box 159 South Lyon
Michigan 48178
Phone: 734-769-1708

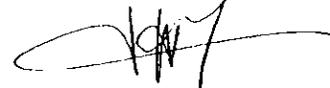
Manufacturer:
YAMAMOTO KOGAKU CO. LTD
Safety and Health Care Division
25-8, Chodo - 3, Higashi-OSAKA City
OSAKA 577 - JAPAN

3- LASER JOULEMETER

model: NOVA - DISPLAY
Head model: PD300-3W

Ophir Optronics, Inc.
200 Corporate Place # 7
Peabody,
MA. 01960
U.S.A.
Phone: (508) 535-5777
Fax: (508) 535-5999

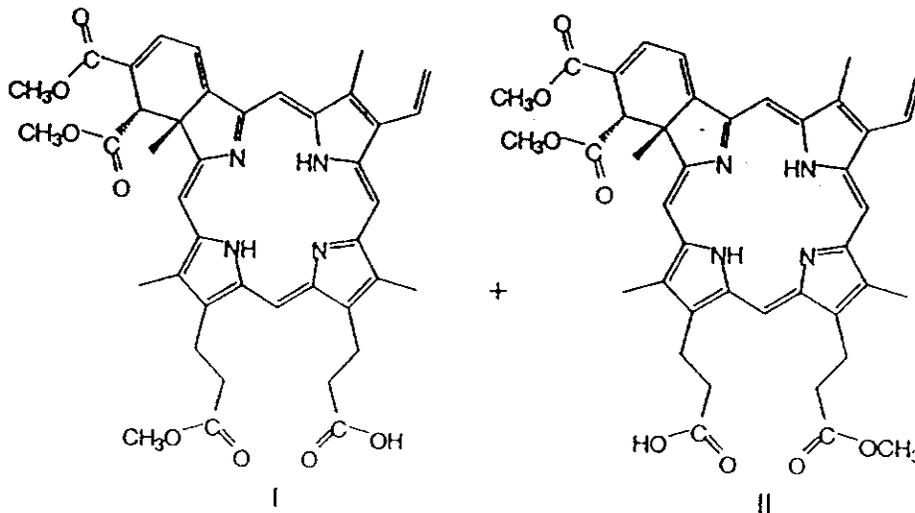
VALIDATION SHEET

SOFTWARE VERSION	Version: 4.xx
Publishing date	March 2006
Revision	March 2006
Written by F. LOYAL	
Checked by Pa. QUERO.	
Validated by C. CHABRIER.	

VISUDYNE™
(verteporfin for injection)

DESCRIPTION

VISUDYNE™ (verteporfin for injection) is a light activated drug used in photodynamic therapy. The finished drug product is a lyophilized dark green cake. Verteporfin is a 1:1 mixture of two regioisomers (I and II), represented by the following structures:



The chemical names for the verteporfin regioisomers are:

9-methyl (I) and 13-methyl (II) *trans*-(±)-18-ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-23*H*, 25*H*-benzo[*b*]porphine-9,13-dipropionate

The molecular formula is $C_{41}H_{42}N_4O_8$ with a molecular weight of approximately 718.8.

Each mL of reconstituted VISUDYNE contains:

ACTIVE: Verteporfin, 2 mg

INACTIVES: Lactose, egg phosphatidylglycerol, dimyristoyl phosphatidylcholine, ascorbyl palmitate and butylated hydroxytoluene

CLINICAL PHARMACOLOGY

Mechanism of Action

VISUDYNE therapy is a two-stage process requiring administration of both verteporfin for injection and nonthermal red light.

Verteporfin is transported in the plasma primarily by lipoproteins. Once verteporfin is activated by light in the presence of oxygen, highly reactive, short-lived singlet oxygen and reactive oxygen radicals are generated. Light activation of verteporfin results in local damage to neovascular endothelium, resulting in vessel occlusion. Damaged endothelium is known to release procoagulant and vasoactive factors through the lipo-oxygenase (leukotriene) and cyclo-oxygenase (eicosanoids such as thromboxane) pathways, resulting in platelet aggregation, fibrin clot formation and vasoconstriction. Verteporfin appears to somewhat preferentially accumulate in neovasculature, including choroidal neovasculature. However, animal models indicate that the drug is also present in the retina. Therefore, there may be collateral damage to retinal structures following photoactivation including the retinal pigmented epithelium and outer nuclear layer of the retina. The temporary occlusion of choroidal neovascularization (CNV) following VISUDYNE therapy has been confirmed in humans by fluorescein angiography.

Pharmacokinetics

Following intravenous infusion, verteporfin exhibits a bi-exponential elimination with a terminal elimination half-life of approximately 5-6 hours. The extent of exposure and the maximal plasma concentration are proportional to the dose between 6 and 20 mg/m². At the intended dose, pharmacokinetic parameters are not significantly affected by gender.

Verteporfin is metabolized to a small extent to its diacid metabolite by liver and plasma esterases. NADPH-dependent liver enzyme systems (including the cytochrome P450 isozymes) do not appear to play a role in the metabolism of verteporfin. Elimination is by the fecal route, with less than 0.01% of the dose recovered in urine.

In a study of patients with mild hepatic insufficiency (defined as having two abnormal hepatic function tests at enrollment), AUC and C_{max} were not significantly different from the control group, half-life however was significantly increased by approximately 20%.

Clinical Studies

Two adequate and well-controlled, double-masked, placebo-controlled, randomized studies were conducted in patients with classic-containing subfoveal CNV secondary to age-related macular degeneration. A total of 609 patients (VISUDYNE 402, placebo 207) were enrolled in these two studies. A planned analysis of safety and efficacy was conducted at 1 year, with 94% of patients completing that portion of the study. During these studies, retreatment was allowed every 3 months if fluorescein angiograms showed any recurrence or persistence of leakage. The placebo control (sham treatment) consisted of intravenous administration of Dextrose 5% in Water, followed by light application identical to that used for VISUDYNE therapy.

The difference between treatment groups statistically favored VISUDYNE at the 1-year analysis for visual acuity endpoints.

The subgroup of patients with predominantly classic CNV lesions was more likely to exhibit a treatment benefit (N=243; VISUDYNE 159, placebo 84). Predominantly classic CNV lesions were defined as those in which the classic component comprised 50% or more of the area of the entire lesion. For the primary efficacy endpoint (percentage of patients who lost less than 3 lines of visual acuity), these patients showed a difference of 28% between treatment groups (67% for VISUDYNE patients compared to 39% for placebo patients, $P < .001$). Severe vision loss (≥ 6 lines of visual acuity from baseline) was experienced by only 12% of VISUDYNE-treated patients compared to 33% of placebo-treated patients.

Patients with predominantly classic CNV lesions that did not contain occult CNV exhibited the greatest benefit (N=134; VISUDYNE 90, placebo 44). These patients demonstrated a 49% difference between treatment groups when assessed by the < 3 lines-lost definition (77% vs. 27%). Severe vision loss (≥ 6 lines of visual acuity from baseline) was experienced by only 10% of VISUDYNE-treated patients compared to 41% of placebo-treated patients.

Older patients (≥ 75 years), patients with dark irides, patients with occult lesions or patients with less than 50% classic CNV were less likely to benefit from VISUDYNE therapy.

The safety and efficacy of VISUDYNE beyond 2 years have not been demonstrated.

INDICATIONS AND USAGE

VISUDYNE therapy is indicated for the treatment of age-related macular degeneration in patients with predominantly classic subfoveal choroidal neovascularization.

CONTRAINDICATIONS

VISUDYNE is contraindicated for patients with porphyria or a known hypersensitivity to any component of this preparation.

WARNINGS

Following injection with VISUDYNE, care should be taken to avoid exposure of skin or eyes to direct sunlight or bright indoor light for 5 days. In the event of extravasation during infusion, the extravasation area must be thoroughly protected from direct light until the swelling and discoloration have faded in order to prevent the occurrence of a local burn which could be severe. If emergency surgery is necessary within 48 hours after treatment, as much of the internal tissue as possible should be protected from intense light.

Patients who experience severe decrease of vision of 4 lines or more within 1 week after treatment should not be retreated, at least until their vision completely recovers to pretreatment levels and the potential benefits and risks of subsequent treatment are carefully considered by the treating physician.

Use of incompatible lasers that do not provide the required characteristics of light for the photoactivation of VISUDYNE could result in incomplete treatment due to partial photoactivation of VISUDYNE, overtreatment due to overactivation of VISUDYNE, or damage to surrounding normal tissue.

PRECAUTIONS

General

Standard precautions should be taken during infusion of VISUDYNE to avoid extravasation. Examples of standard precautions include, but are not limited to:

- A free-flowing intravenous (IV) line should be established before starting VISUDYNE infusion and the line should be carefully monitored.
- Due to the possible fragility of vein walls of some elderly patients, it is strongly recommended that the largest arm vein possible, preferably antecubital, be used for injection.
- Small veins in the back of the hand should be avoided.

If extravasation does occur, the infusion should be stopped immediately and cold compresses applied (see Warnings).

VISUDYNE therapy should be considered carefully in patients with moderate to severe hepatic impairment since there is no clinical experience with verteporfin in such patients.

There is no clinical data related to the use of VISUDYNE in anesthetized patients. At a >10-fold higher dose given by bolus injection to anesthetized pigs, verteporfin caused severe hemodynamic effects, including death, probably as a result of complement activation. These effects were diminished or abolished by pretreatment with antihistamine and they were not seen in conscious pigs or in any other species, whether conscious or under general anesthesia.

Information for Patients

Patients who receive VISUDYNE will become temporarily photosensitive after the infusion. Patients should wear a wrist band to remind them to avoid direct sunlight for 5 days. During that period, patients should avoid exposure of unprotected skin, eyes or other body organs to direct sunlight or bright indoor light. Sources of bright light include, but are not limited to, tanning salons, bright halogen lighting and high power lighting used in surgical operating rooms or dental offices.

If treated patients must go outdoors in daylight during the first 5 days after treatment, they should protect all parts of their skin and their eyes by wearing protective clothing and dark sunglasses. UV sunscreens are not effective in protecting against photosensitivity reactions because photoactivation of the residual drug in the skin can be caused by visible light.

Patients should not stay in the dark and should be encouraged to expose their skin to ambient indoor light, as it will help inactivate the drug in the skin through a process called photobleaching.

Drug Interactions

Drug interaction studies in humans have not been conducted with VISUDYNE.

Verteporfin is rapidly eliminated by the liver, mainly as unchanged drug. Metabolism is limited and occurs by liver and plasma esterases. Microsomal cytochrome P450 does not appear to play a role in verteporfin metabolism.

Based on the mechanism of action of verteporfin, many drugs used concomitantly could influence the effect of VISUDYNE therapy. Possible examples include the following:

Calcium channel blockers, polymyxin B or radiation therapy could enhance the rate of VISUDYNE uptake by the vascular endothelium. Other photosensitizing agents (e.g., tetracyclines, sulfonamides, phenothiazines, sulfonylurea hypoglycemic agents, thiazide, diuretics and griseofulvin) could increase the potential for skin photosensitivity reactions. Compounds that quench active oxygen species or scavenge radicals, such as dimethyl sulfoxide, β -carotene, ethanol, formate and mannitol, would be expected to decrease VISUDYNE activity. Drugs that decrease clotting, vasoconstriction or platelet aggregation, e.g., thromboxane A₂ inhibitors, could also decrease the efficacy of VISUDYNE therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted to evaluate the carcinogenic potential of verteporfin.

Photodynamic therapy (PDT) as a class has been reported to result in DNA damage including DNA strand breaks, alkali-labile sites, DNA degradation, and DNA-protein cross links which may result in chromosomal aberrations, sister chromatid exchanges (SCE), and mutations. In addition, other photodynamic therapeutic agents have been shown to increase the incidence of SCE in Chinese hamster ovary (CHO) cells irradiated with visible light and in Chinese hamster lung fibroblasts irradiated with near UV light, increase mutations and DNA-protein cross-linking in mouse L5178 cells, and increase DNA-strand breaks in malignant human cervical carcinoma cells, but not in normal cells. Verteporfin was not evaluated in these latter systems. It is not known how the potential for DNA damage with PDT agents translates into human risk.

No effect on male or female fertility has been observed in rats following intravenous administration of verteporfin for injection up to 10 mg/kg/day (approximately 60 and 40 fold human exposure at 6 mg/m² based on AUC_{inf} in male and female rats, respectively).

Pregnancy

Teratogenic Effects: Pregnancy Category C.

Rat fetuses of dams administered verteporfin for injection intravenously at ≥ 10 mg/kg/day during organogenesis (approximately 40 fold human exposure at 6 mg/m² based on AUC_{inf} in female rats) exhibited an increase in the incidence of anophthalmia/microphthalmia. Rat fetuses of dams administered 25 mg/kg/day (approximately 125 fold the human exposure at 6 mg/m² based on AUC_{inf} in female rats) had an increased incidence of wavy ribs and anophthalmia/microphthalmia.

In pregnant rabbits, a decrease in body weight gain and food consumption was observed in animals that received verteporfin for injection intravenously at ≥ 10 mg/kg/day during organogenesis. The no observed adverse effect level (NOAEL) for maternal toxicity was 3 mg/kg/day (approximately 7 fold human exposure at 6 mg/m² based on body surface area). There were no teratogenic effects observed in rabbits at doses up to 10 mg/kg/day.

There are no adequate and well-controlled studies in pregnant women. VISUDYNE should be used during pregnancy only if the benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether verteporfin for injection is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VISUDYNE is administered to a women who is nursing.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Approximately 90% of the patients treated with VISUDYNE in the clinical efficacy trials were over the age of 65. A reduced treatment effect was seen with increasing age.

ADVERSE REACTIONS

The most frequently reported adverse events to VISUDYNE are headaches, injection site reactions (including extravasation and rashes) and visual disturbances (including blurred vision, decreased visual acuity and visual field defects). These events occurred in approximately 10-20% of patients. The following events, listed by Body System, were reported more frequently with VISUDYNE therapy than with placebo therapy and occurred in 1-10% of patients:

Ocular Treatment Site:	Cataracts, conjunctivitis/conjunctival injection, dry eyes, ocular itching, severe vision loss, subconjunctival, subretinal or vitreous hemorrhage
Body as a Whole:	Asthenia, back pain (primarily during infusion), fever, flu syndrome, photosensitivity
Cardiovascular:	Atrial fibrillation, hypertension, peripheral vascular disorder, varicose veins
Dermatologic:	Eczema

Digestive:	Constipation, gastrointestinal cancers, nausea
Hemic and Lymphatic:	Anemia, white blood cell count decreased, white blood cell count increased
Hepatic:	Elevated liver function tests
Metabolic/Nutritional:	Albuminuria, creatinine increased
Musculoskeletal:	Arthralgia, arthrosis, myasthenia
Nervous system:	Hypesthesia, sleep disorder, vertigo
Respiratory:	Pharyngitis, pneumonia
Special Senses:	Decreased hearing, diplopia, lacrimation disorder
Urogenital:	Prostatic disorder

Severe vision decrease, equivalent of 4 lines or more, within 7 days after treatment has been reported in 1-4% of patients. Partial recovery of vision was observed in many patients. Photosensitivity reactions occurred in the form of skin sunburn following exposure to sunlight. The higher incidence of back pain in the VISUDYNE group occurred primarily during infusion.

OVERDOSAGE

Overdose of drug and/or light in the treated eye may result in nonperfusion of normal retinal vessels with the possibility of severe decrease in vision that could be permanent. An overdose of drug will also result in the prolongation of the period during which the patient remains photosensitive to bright light. In such cases, it is recommended to extend the photosensitivity precautions for a time proportional to the overdose.

DOSAGE AND ADMINISTRATION

A course of VISUDYNE therapy is a two-step process requiring administration of both drug and light.

The first step is the intravenous infusion of VISUDYNE. The second step is the activation of VISUDYNE with light from a nonthermal diode laser.

The physician should re-evaluate the patient every 3 months and if choroidal neovascular leakage is detected on fluorescein angiography, therapy should be repeated.

Lesion Size Determination

The greatest linear dimension (GLD) of the lesion is estimated by fluorescein angiography and color fundus photography. All classic and occult CNV, blood and/or blocked fluorescence, and any serous detachments of the retinal pigment epithelium should be included for this measurement. Fundus cameras with magnification within the range of 2.4-2.6X are recommended. The GLD of the lesion on the fluorescein angiogram must be corrected for the magnification of the fundus camera to obtain the GLD of the lesion on the retina.

Spot Size Determination

The treatment spot size should be 1000 microns larger than the GLD of the lesion on the retina to allow a 500 micron border, ensuring full coverage of the lesion. The maximum spot size used in the clinical trials was 6400 microns.

The nasal edge of the treatment spot must be positioned at least 200 microns from the temporal edge of the optic disc, even if this will result in lack of photoactivation of CNV within 200 microns of the optic nerve.

VISUDYNE Administration

Reconstitute each vial of VISUDYNE with 7 mL of sterile Water for Injection to provide 7.5 mL containing 2 mg/mL. Reconstituted VISUDYNE must be protected from light and used within 4 hours. It is recommended that reconstituted VISUDYNE be inspected visually for particulate matter and discoloration prior to administration. Reconstituted VISUDYNE is an opaque dark green solution.

The volume of reconstituted VISUDYNE required to achieve the desired dose of 6 mg/m² body surface area is withdrawn from the vial and diluted with 5% Dextrose for Injection to a total infusion volume of 30 mL. The full infusion volume is administered intravenously over 10 minutes at a rate of 3 mL/minute, using an appropriate syringe pump and in-line filter.

Precautions should be taken to prevent extravasation at the injection site. If extravasation occurs, protect the site from light (See Precautions).

Light Administration

Initiate 689 nm wavelength laser light delivery to the patient 15 minutes after the start of the 10-minute infusion with VISUDYNE.

Photoactivation of VISUDYNE is controlled by the total light dose delivered. In the treatment of choroidal neovascularization, the recommended light dose is 50 J/cm² of neovascular lesion administered at an intensity of 600 mW/cm². This dose is administered over 83 seconds.

Light dose, light intensity, ophthalmic lens magnification factor and zoom lens setting are important parameters for the appropriate delivery of light to the predetermined treatment spot. Follow the laser system manuals for procedure set up and operation.

The laser system must deliver a stable power output at a wavelength of 689±3 nm. Light is delivered to the retina as a single circular spot via a fiber optic and a slit lamp, using a suitable ophthalmic magnification lens.

The following laser systems have been tested for compatibility with VISUDYNE and are approved for delivery of a stable power output at a wavelength of 689±3 nm:

Coherent Opal Photoactivator Laser Console and LaserLink Adapter,
Manufactured by Coherent, Inc., Santa Clara, CA

Zeiss VISULAS 690s laser and VISULINK PDT adapter,
Manufactured by Carl Zeiss Inc., Thornwood, NY

Concurrent Bilateral Treatment

The controlled trials only allowed treatment of one eye per patient. In patients who present with eligible lesions in both eyes, physicians should evaluate the potential benefits and risks of treating both eyes concurrently. If the patient has already received previous VISUDYNE therapy in one eye with an acceptable safety profile, both eyes can be treated concurrently after a single administration of VISUDYNE. The more aggressive lesion should be treated first, at 15 minutes after the start of infusion. Immediately at the end of light application to the first eye, the laser settings should be adjusted to introduce the treatment parameters for the second eye, with the same light dose and intensity as for the first eye, starting no later than 20 minutes from the start of infusion.

In patients who present for the first time with eligible lesions in both eyes without prior VISUDYNE therapy, it is prudent to treat only one eye (the most aggressive lesion) at the first course. One week after the first course, if no significant safety issues are identified, the second eye can be treated using the same treatment regimen after a second VISUDYNE infusion. Approximately 3 months later, both eyes can be evaluated and concurrent

treatment following a new VISUDYNE infusion can be started if both lesions still show evidence of leakage.

HOW SUPPLIED

VISUDYNE is supplied in a single use glass vial with a gray bromobutyl stopper and aluminum flip-off cap. It contains a lyophilized cake with 15 mg verteporfin. The product is intended for intravenous injection only.

Spills and Disposal

Spills of VISUDYNE should be wiped up with a damp cloth. Skin and eye contact should be avoided due to the potential for photosensitivity reactions upon exposure to light. Use of rubber gloves and eye protection is recommended. All materials should be disposed of properly.

Accidental Exposure

Because of the potential to induce photosensitivity reactions, it is important to avoid contact with the eyes and skin during preparation and administration of VISUDYNE. Any exposed person must be protected from bright light (See Warnings).

NDC 58768-150-15

Store VISUDYNE between 20°C and 25°C (68°F-77°F).

Rx Only

Manufactured by:

Parkedale Pharmaceuticals, Inc.
Rochester, MI 48307

For:

QLT PhotoTherapeutics, Inc.
Seattle, WA 98101

RG-99042
VISUDYNE™ (verteporfin for injection)

US Package Insert
April 7, 2000

Co-developed and Distributed by:

CIBA Vision
A Novartis Company
Duluth, GA 30097